Journal of the American College of Cardiology
Vol. 34, No. 4, 1999

ISSN 0735-1097/99/$20.00
Published by Elsevier Science Inc.
PII S0735-1097(99)00343-5

The Influence of Low Afterload on the Nature of the Stress-Velocity Relationship

Daniël De Wolf, MD, PhD, Luc Foubert, MD,* Yves Van Belleghem, MD,† Kathy Mareels, MD,* Dirk Matthys, MD, PhD, Henri Verhaaren, FACC, MD, PhD, Guido Van Nooten, MD, PhD†
Ghent, Belgium

OBJECTIVES Correct assessment of contractility by conventional methods during manipulation of afterload is often disappointing. To this purpose, the stress-velocity relationship offers assessment of contractility at different levels of afterload. We decided to study the influence of afterload on the nature of the stress-velocity relation.

BACKGROUND Although linear at baseline conditions in a population older than two years, data in newborns or after administration of low-dose dobutamine suggest a different nature of this relationship at low afterload.

METHODS Ten healthy piglets (five to six weeks; 11 to 13 kg) were studied. End-systolic meridional wall stress (ESWS) and rate-corrected velocity of circumferential fiber shortening (VcFc) were measured in these piglets at baseline, after balloon occlusion of the descending aorta, and at nitroprusside infusion rates of 1, 2 and 5 μg/kg/min. To eliminate inotropic influences mediated by reflex tachycardia, we subsequently studied five piglets and six adult pigs after bilateral cervical vagotomy.

RESULTS The ESWS changed from a baseline mean of 50 g/cm^2 to 137 g/cm^2 after balloon occlusion and to 19 g/cm^2 at 5 μg/kg/min of nitroprusside. The VcFc changed from 1.19 c/s (circumference/second) to values of 0.9 c/s and 1.73 c/s, respectively. The ensuing stress-velocity regression line proved to be curvilinear instead of linear. The steeper slope at low afterload could suggest enhanced contractility compared to expected values had the relationship been linear.

CONCLUSIONS Data from young piglets and adult pigs suggest a curvilinear relationship of the stress-velocity relationship. This could probably explain some of the "hypercontractile states" encountered in conditions with low afterload. (J Am Coll Cardiol 1999;34:1219–25) © 1999 by the American College of Cardiology

Fractional shortening (FS) and ejection fraction (EF) remain the most widely used echocardiographic indexes of left ventricular (LV) performance. They can be readily calculated from two-dimensional and M-mode echocardiogram images and are obtainable in most patients (1). Because they measure global pump performance both of these indexes are sensitive to alterations in loading conditions and heart rate (2,3). Their utility to assess muscle function or contractility becomes questionable when disease processes or natural physiologic states result in significant alterations in these variables (2–4).

The stress-velocity relation obtained by noninvasive evaluation (the relationship between heart rate-corrected velocity of circumferential fiber shortening [VcFc] and end-systolic meridional wall stress [ESWS] has been postulated to assess contractility independent of loading conditions (3,5,6). Normal values for this preload-independent relation have been established, with a good reproducibility in children older than two years (7,8). In this age group the relation seems to be linear, with shifts of the regression line with changes of contractility (3).

For infants, however, especially below six months of age, the relationship seems to follow a steeper regression line than in older children (8–10). We found that after dobutamine infusion in normal children and young adults, the nature of this stress-velocity relationship changed at low afterload and became steeper or even curvilinear (11). Studies in young pigs, using propanolol and dobutamine, also question the linearity of the stress-velocity relation in a state of low afterload (12).

To assess the influence of low afterload on the nature of the stress-velocity relationship without interfering directly with contractility (as was the case with dobutamine), we studied the stress-velocity relationship at different levels of afterload in young piglets and adult pigs.

METHODS

Population. Ten piglets (age five to six weeks; 5 m, 5 f; 11 to 13 kg) were studied under general anesthesia. All were in

From the Department of Pediatrics, Division of Pediatric Cardiology; *Department of Anesthesia, Division of Cardiac Anesthesia; and †Department of Surgery, Division of Cardiac Surgery, University Hospital UZGhent, Ghent, Belgium.
Manuscript received September 11, 1998; revised manuscript received May 5, 1999, accepted June 22, 1999.

Abbreviations and Acronyms

ANOVA	=	analysis of variance
BP	=	blood pressure
CO	=	cardiac output
ECG	=	electrocardiogram
EF	=	ejection fraction
ESWS	=	end-systolic meridional wall stress
ET	=	ejection time
ETc	=	rate-corrected LV ejection time
FS	=	fractional shortening
LV	=	left ventricular
LVID	=	left ventricular internal diameter
LVPW	=	left ventricular posterior wall thickness
SVR	=	systemic vascular resistance
VcFc	=	rate-corrected velocity of circumferential fiber shortening

good health without overt clinical signs of disease. Five other piglets (age seven to eight weeks; 3 m, 2 f; 13 to 16 kg) and six adult pigs (age three months; 3 m, 3 f; 40 to 45 kg) were subsequently studied after bilateral cervical vagotomy.

Data collection. The pigs and piglets, studied under general anesthesia, were premedicated with azaperone (8 mg/kg IM) and anesthetized with sodium thiopental (10 mg/kg IV) and pancuronium (0.15 mg/kg IV). The animals were intubated and mechanically ventilated (FiO_2 40%). Anesthesia was maintained with sufentanil (0.03 μg/kg/min), propofol (200 μg/kg/min) and pancuronium (7 μg/kg/min). Arterial pressures were measured invasively by means of a catheter indwelling in the ascending aorta by cannulation of right or left carotid artery. Cardiac output was measured by means of a thermodilution catheter (Baxter, Irvine, California) introduced through right or left jugular vein. Occlusion of the descending aorta was performed by inflating the balloon of a 7F Swan-Ganz catheter (Baxter) introduced through cannulation of the right femoral artery. Sodium nitroprusside was given through a vein in the piglets' ears. Echocardiographic examinations were performed with a Hewlett-Packard Sonos 500 using a 3.5-MHz transducer. Electrocardiogram (ECG) (peripheral leads) was continuously monitored. In five piglets and six adult pigs a bilateral cervical vagotomy was performed surgically and echocardiographic measurements were performed after reaching a stable heart rate and blood pressure (BP). The experiments were performed in accordance with institutional guidelines for animal research, equivalent to the American Heart Association position.

Data analysis. The following measurements were obtained at systole and end-diastole: LV short-axis diameters (LVIDsystole and LVIDdiastole) and posterior wall thickness (LVPWs and LVPWd) according to standard rules (1). Left ventricular ejection time (ET) was derived from the invasive aortic pulse signal, and rate-corrected to a heart rate of 60 beats/min rate-corrected LV ejection time (ETc) by dividing ET by the square root of the R-R interval of the preceding cardiac cycle.

Fractional shortening (FS [%] = [(LVIDd−LVIDs)/LVIDd]) and heart-rate-corrected VcF (VcFc[c/s] = FS/ETc) were calculated.

Left ventricular end-systolic meridional wall stress or ESWS = ([1.35 × P × LVIDsystole]/(4 × LVPWsystole × (1+LVPWsystole/LVIDsystole))) was determined according to Grossman et al. (13), where P means end-systolic BP. Systemic vascular resistance was calculated using mean arterial BP and cardiac output (CO). Sodium nitroprusside was administered by continuous infusion in a large vein. The administration was subdivided in three stages: 1) with an infusion rate of 1 μg/kg/min; 2) at a rate of 2 μg/kg/min; and 3) at 5 μg/kg/min. Echocardiographic measurements were performed at baseline and after reaching a steady state in each stage. After balloon occlusion of the descending aorta, echocardiographic measurements and measurement of end-systolic BP were performed within eight beats following balloon inflation. The same observer performed all echocardiographic measurements.

In five piglets and six adult pigs the same measurements were performed after bilateral cervical vagotomy. After bilateral vagotomy at least part of the afferent pathways that control reflex autonomic stimulation seems to be abolished. Even without pharmacologic sympathetic blockade, cervical vagotomy eliminates reflex tachycardia and probably most of the other autonomic reflexes capable of increasing contractility in response to induced hypotension (14,15). To reach a sufficiently "low afterload" state in the adult pig group we added a fourth stage of sodium nitroprusside infusion in this particular group at a rate of 10 μg/kg/min.

Statistical analysis. The differences at every stage of nitroprusside infusion toward baseline were compared with an analysis of variance (ANOVA) by repeated measures. A p value < 0.01 was considered statistically significant. Regression analysis was performed to assess the correct relation between wall stress and VcFc, and the "best fit" stress-velocity relation and curve were assessed by the Levenberg-Marquardt least-squares method, using Excel and Sigmastat and Sigma-plot computer algorithms.

RESULTS

The results of the nonvagotomized piglets are presented in Table 1 as mean ± 2 SD. No serious adverse effects were noted, and all subjects could be included in the study.

Pressure. Balloon occlusion of the descending aorta increased systolic, diastolic, end-systolic BP, ESWS and SVR (systemic vascular resistance). Sodium nitroprusside infusion decreased all these variables.

LV dimensions. Balloon occlusion increased LVIDsystole and decreased LVPWsystole (LV posterior wall thickness), and sodium nitroprusside decreased LVIDsystole and in-

Table 1. Data at Different Levels of Afterload for 10 Piglets

		Baseline	Nitro 1	Nitro 2	Nitro 5	Balloon
Diastolic BP	mm Hg	59 ± 20	59 ± 30	53 ± 35	49 ± 29	75 ± 51*
Systolic BP	mm Hg	101 ± 28	97 ± 35	89 ± 36	84 ± 32	146 ± 57*
End-systolic BP	mm Hg	83 ± 31	81 ± 36	74 ± 34	68 ± 34	118 ± 49*
LVIDdiastole	mm	32 ± 9	31 ± 6	31 ± 8	30 ± 9	34 ± 6 NS
LVIDsystole	mm	20 ± 6	19 ± 7	17 ± 5	15 ± 7	25 ± 6*
LVPWdiastole	mm	5 ± 2	5 ± 2	5 ± 2	5 ± 2	4 ± 2 NS
LVPWsystole	mm	9 ± 3	9 ± 3	10 ± 4	12 ± 3	6 ± 2*
LVPW thickening	%	79 ± 35	89 ± 56	120 ± 104	123 ± 76	41 ± 62*
ESWS	g/cm^2	50 ± 44	43 ± 44	30 ± 38	19 ± 24	137 ± 110*
VcFc	c/s	1.19 ± 0.44	1.29 ± 0.52	1.54 ± 0.56	1.73 ± 0.64	0.9 ± 0.32*
Cardiac output	l/min	1.9 ± 0.9	2.15 ± 1.2	2.29 ± 1.3	2.43 ± 1.5	1.19 ± 0.9*
Systemic vascular resistance	dyne·secs·cm^{-5}	3363 ± 3236	3070 ± 3902	2670 ± 3498	2435 ± 3506	7698 ± 7092*
Fractional shortening	%	35 ± 12	38 ± 14	44 ± 16	49 ± 22	26 ± 12*
Heart rate	beats/min	117 ± 46	122 ± 46	123 ± 45	131 ± 62	109 ± 41*

*Significant differences according to ANOVA (analysis of variance) by repeated measures with $p < 0.01$ considered statistically significant. Data expressed as mean ± 2 SD. Nitro = nitroprusside.

creased LVPWsystole. Both LVIDdiastole and LVPWdiastole (LV posterior wall thickness) did not change.

Performance. Rate-corrected velocity of circumferential fiber shortening, CO and FS decreased during balloon occlusion and increased during sodium nitroprusside infusion.

Heart rate. Heart rate decreased during balloon occlusion and increased during sodium nitroprusside infusion rate of 5 μg/kg/min.

The regression line of the relationship between ESWS at every test condition (baseline, sodium nitroprusside, balloon occlusion) was plotted for the overall population (Fig. 1).

We subsequently included five piglets and six adult pigs studied after bilateral cervical vagotomy to eliminate reflex tachycardia and age as possible interferences with the inotropic response to low afterload. The results are presented in Tables 2 and 3 as mean ± 2 SD. After vagotomy we saw a rise of heart rate, with a mean of 20 beats/min and an increase in systolic, diastolic, and end-systolic BP.

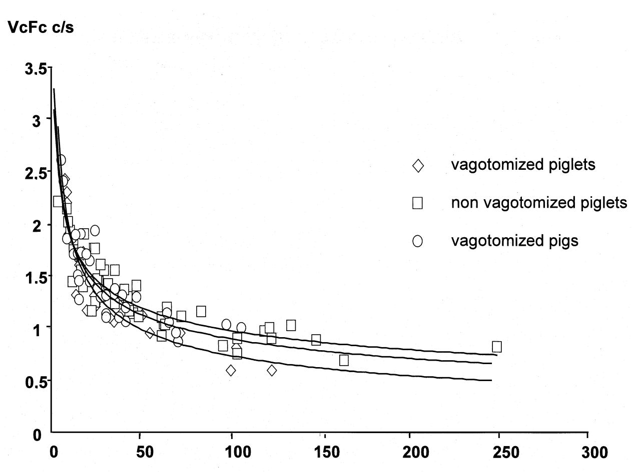

Figure 1. Regression lines of the relation between end-systolic meridional wall stress (ESWS) and velocity of circumferential fiber shortening (VcFc) at different levels of afterload manipulation for nonvagotomized piglets, vagotomized piglets and vagotomized pigs, showing a comparable curve.

Pressure. Balloon occlusion of the descending aorta increased systolic, diastolic, end-systolic BP, ESWS and SVR in both groups. Sodium nitroprusside infusion decreased all these variables in both groups.

LV dimensions. Balloon occlusion increased LVIDdiastole, LVIDsystole, and decreased LVPWsystole (LV posterior wall thickness), and sodium nitroprusside infusion decreased LVIDdiastole, LVIDsystole, and increased LVPWsystole in both groups. The LVPWdiastole (LV posterior wall thickness) did not change in the piglet group but decreased during balloon occlusion and increased during sodium nitroprusside infusion in the adult pig group.

Performance. Both VcFc and FS decreased during balloon occlusion and increased during sodium nitroprusside infusion in both groups. The CO level did not change.

Heart rate. Heart rate did not change. The influence of the test protocol on the measured variables was comparable to the nonvagotomized group except for constant heart rate, decreased variation of CO and increased influence of sodium nitroprusside on systolic, diastolic and end-systolic BP, suggesting efficient sympathetic blockade.

For the adult pig group we included measurements at a sodium nitroprusside infusion rate of 10 μg/kg/min. Diastolic BP was 39 ± 7 mm Hg; systolic BP was 75 ± 20 mm Hg; end-systolic BP was 54 ± 14 mm Hg; ESWS 12 ± 9 g/cm^2; SVR 1206 ± 181 dyne·secs·cm^{-5}; LVIDd 38 ± 7 mm; LVIDs 10 ± 9 mm; LVPWs 17 ± 3 mm;

Table 2. Piglet Data After Vagotomy

		Baseline	Nitro 1	Nitro 2	Nitro 5	Balloon
Diastolic BP	mm Hg	78 ± 26	68 ± 15	64 ± 23	53 ± 21	92 ± 20*
Systolic BP	mm Hg	107 ± 41	58 ± 26	90 ± 25	77 ± 27	141 ± 35*
End-systolic BP	mm Hg	95 ± 32	83 ± 22	77 ± 24	69 ± 22	116 ± 22*
LVIDdiastole	mm	26 ± 6	27 ± 3	25 ± 5	23 ± 5	29 ± 6*
LVIDsystole	mm	16 ± 2	14 ± 4	13 ± 4	11 ± 2	21 ± 2*
LVPWdiastole	mm	5 ± 2	5 ± 2	5 ± 2	6 ± 2	4 ± 1 NS
LVPWsystole	mm	8 ± 4	10 ± 3	11 ± 2	12 ± 2	7 ± 3*
LVPW thickening	%	62 ± 14	91 ± 66	104 ± 84	95 ± 52	67 ± 46*
ESWS	g/cm^2	46 ± 23	23 ± 12	18 ± 11	10 ± 5	91 ± 54*
VcFc	c/s	1.14 ± 0.2	1.39 ± 0.6	1.45 ± 0.5	2.0 ± 1	0.78 ± 0.3*
Cardiac output	l/min	2.1 ± 1	1.9 ± 1	1.9 ± 1	2.0 ± 1	1.9 ± 1 NS
Systemic vascular resistance	dyne·secs·cm^{-5}	3550 ± 1670	3454 ± 1520	3317 ± 1736	2764 ± 1424	4819 ± 1900*
Fractional shortening	%	39 ± 4	47 ± 10	48 ± 7	54 ± 8	27 ± 14*
Heart rate	beats/min	148 ± 38	145 ± 44	145 ± 42	145 ± 46	146 ± 41 NS

Data expressed as mean ± 2 SD. Nitro = nitroprusside.

LVPWd 11 ± 5 mm; %LVPW thickening 59 ± 62%; VcFc 1.9 ± 1 c/s; FS 48 ± 18%; CO 3.4 ± 1.3 1/min; and heart rate 95 ± 32 beats/min (all values expressed as mean ± 2 SD).

The regression line of the relationship between ESWS at every test condition (baseline, sodium nitroprusside, balloon occlusion) was plotted for both vagotomized groups (Fig. 1). The "best fit" regression line of the relationship between ESWS and VcFc for the overall population under different test conditions (data of baseline, sodium nitroprusside infusion and balloon occlusion gathered) was curvilinear with a steep slope at low afterload (Fig. 1). The regression line of every individual piglet at the different test conditions showed a similar configuration. The equation of this curvilinear relationship for the overall piglet population was: VcFc = 3.7852 $ESWS^{-0.2944}$ with $R^2 = 0.8182$. We found comparable configurations of the regression lines in the group of the vagotomized piglets (VcFc = 5.2932 $ESWS^{-0.4282}$ with $R^2 = 0.8894$) and pigs (VcFc = 4.1471 $ESWS^{-0.3324}$ with $R^2 = 0.7851$) (Fig. 1), but for the adult pig group we could only obtain a curvilinear regression line that differed significantly from a linear relation if we included the measurements obtained at a sodium nitroprusside infusion rate of 10 μg/kg/min. Indeed, if we included only baseline values and measurements up to a sodium nitroprusside infusion rate of 5 μg/kg/min, the adult pig group showed a linear fit (Fig. 2), but this represents merely a plateau of an essentially curvilinear relationship (Fig. 1).

DISCUSSION

Aim and background. Estimating the relation between VcFc and ESWS using echocardiographic techniques has widely won acceptance to assess contractility. This was termed the "stress-velocity relation" or the relationship

Table 3. Adult Pig Data After Vagotomy

		Baseline	Nitro 1	Nitro 2	Nitro 5	Balloon
Diastolic BP	mm Hg	79 ± 20	59 ± 14	56 ± 12	46 ± 9	97 ± 42*
Systolic BP	mm Hg	117 ± 14	95 ± 20	93 ± 20	82 ± 18	132 ± 28*
End-systolic BP	mm Hg	105 ± 22	81 ± 18	75 ± 11	63 ± 10	118 ± 20*
LVIDdiastole	mm	43 ± 6	41 ± 8	41 ± 8	39 ± 5	45 ± 5*
LVIDsystole	mm	26 ± 3	25 ± 6	23 ± 6	22 ± 5	30 ± 6*
LVPWdiastole	mm	9 ± 3	10 ± 2	10 ± 2	11 ± 1	8 ± 3*
LVPWsystole	mm	15 ± 2	15 ± 3	15 ± 4	16 ± 3	11 ± 3*
LVPW thickening	%	65 ± 46	48 ± 36	52 ± 58	57 ± 32	43 ± 58 NS
ESWS	g/cm^2	40 ± 11	29 ± 14	24 ± 16	18 ± 10	79 ± 17*
VcFc	c/s	1.3 ± 0.4	1.22 ± 0.2	1.61 ± 0.3	1.77 ± 0.4	1.05 ± 0.3*
Cardiac output	l/min	4.0 ± 1	3.6 ± 1	3.6 ± 0.9	3.6 ± 1	3.8 ± 1 NS
Systemic vascular resistance	dyne·secs·cm^{-5}	1952 ± 530	1671 ± 330	1618 ± 356	1406 ± 298	2391 ± 612*
Fractional shortening	%	40 ± 5	39 ± 5	43 ± 10	44 ± 9	32 ± 9*
Heart rate	beats/min	95 ± 32	96 ± 30	95 ± 31	95 ± 33	95 ± 31 NS

*Data expressed as mean ± 2 SD. Nitro = nitroprusside.

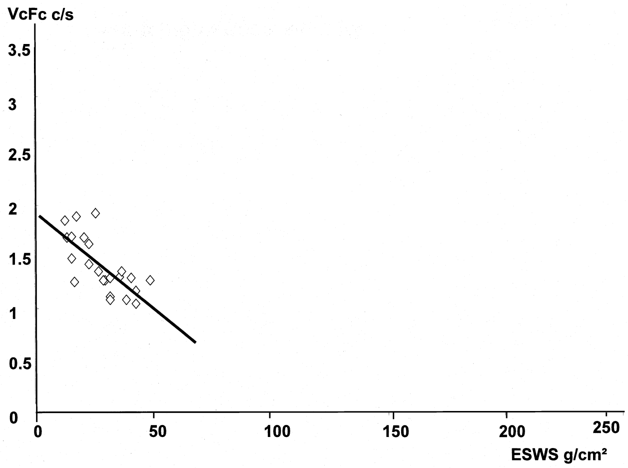

Figure 2. Regression line of the relation between end-systolic wall stress and velocity of circumferential fiber shortening (VcFc) for vagotomized adult pigs after afterload manipulation from baseline to a sodium nitroprusside infusion rate up to 5 μg/kg/min. This relation seems linear, but represents merely a segment of the nonlinear curve as found in Figure 1, in which values at lower afterload obtained during infusion of sodium nitroprusside at a rate of 10 μg/kg/min are included.

between the mean velocity of fiber shortening corrected for heart rate (VcFc, a preload independent variable) and ESWS opposing contraction (3). The stress-velocity relationship was evaluated across a wide range of afterloads and ages. Using current methods, the relation was found to be linear and did not differ in children between two years of age and adults (7,8). A few studies have addressed the stress-velocity relation in newborns or in children below the age of two years (8–10). The findings of these studies showed a much steeper slope and higher *y*-intercept of the regression line in this age group, compared to older children. The hypothesis that the myocardium of newborns and infants has a higher basal inotropic state and a greater sensibility to changes in afterload than the myocardium of older children and adults has been proposed (8). Recently, manipulation of afterload with propanolol and dobutamine in young pigs suggested that the stress-velocity relation could be curvilinear (12). This was also suggested in a human population during low-dose dobutamine stress echocardiography (11,16). However, the problem could not completely be solved owing to two limitations of these previous studies. First was the use of agents simultaneously influencing afterload and contractility (11,12,16), and the second was the cross-sectional design of some of the studies without assessment of the individual relationship between VcFc and wall stress at different levels of afterload (11,16).

Therefore, we studied the relationship between wall stress and VcFc at various levels of afterload using sodium nitroprusside infusions and balloon occlusion of the descending aorta in individual young anesthetized piglets.

Sodium nitroprusside was chosen to decrease afterload because it acts as an endothelium-independent nitric oxide donator with a vasodilator effect on veins and arteries and without any proven important direct inotropic effect on the myocardium.

Nature of the relationship. Neglecting the assumption of a linear relationship between stress and VcFc, we indeed found that a curvilinear regression line offered the "best fit" for the relationship between ESWS and VcFc at different levels of afterload and that the slope of this relationship became very steep at low afterload. This suggests that the mere fact of lowering afterload below a critical point might result in a much higher increase in VcFc or "contractility" than expected from the linear stress-velocity relation found at higher afterload, without any other inotropic stimulus. "Increased contractility" in this discussion signifies a much higher level of VcFc in the low afterload range than would be expected from an extension of the hitherto almost generally accepted linear stress-velocity relationship analogous to the one described for older children (3,7). Indeed, VcFc is shifted upward compared with theoretically expected values (using a linear relationship), reflecting an "increase in contractility" (3,7). But more correctly, if indeed the stress-velocity relationship is curvilinear, this high level of VcFc in the low afterload range merely reflects the "normal contractility" in this low afterload range due to the steep slope of the curve at this level.

Autonomic reflexes. The fact that the curvilinear nature of the regression line did not change in the second and third groups, studied after bilateral cervical vagotomy and thus suppressing the possible inotropic effect of hypotensive-induced autonomic reflexes (14,15), supports the hypothesis of a direct relationship between low afterload and increased velocity of fiber shortening. The possible influence of sympathetic stimulation on the stress-velocity relationship was already discussed before in children, where the highest levels of inotropy were found in sedated and sleeping infants (not subject to acute changes in loading conditions), the least likely group to exhibit excess sympathetic activity under those circumstances (10). The regression line in the three animal groups resembles the curvilinear relationship between ESWS and VcFc after infusion of dobutamine in children with a much higher increase of VcFc at low afterload compared to the increase of VcFc at high afterload despite similar doses of dobutamine (11,16,17). The different behavior of the stress-velocity relationship in neonates (a "low afterload population") can also easily be explained by this phenomenon.

Age. To clarify the question whether young age could be an independent factor responsible for the steeper slope of the stress-velocity relation (enhanced contractility of "immature" myocardium), we studied the relationship in adult pigs. Although the initial results suggested a linear relationship different from the one found in the two piglet groups (Fig. 2), lowering afterload to the same extent as in those two piglet groups using a supplementary sodium nitroprussside infusion rate of 10 μg/kg/min revealed a comparable curvilinear stress-velocity relationship with a steep increase of the slope below a "critical point" of ESWS.

Physiologic and clinical relevance. These data confirm previous reports of the curvilinear nature of the stress-velocity relationship using comparable methods (12,16). The contradiction with numerous other reports suggesting a linear stress-velocity relationship could be explained by the scarcity of data at low afterload in those investigations (3,5–8,18–21). Under these circumstances one cannot expect to find the steeper slope of the stress-velocity curve at low afterload. This phenomenon can be fully appreciated in the group of adult pigs in this study: the stress-velocity curve remains linear until we lower afterload further by increasing the sodium nitroprusside rate to 10 μg/kg/min (Figs. 1 and 2). Earlier reports addressing the force-velocity relationship using other methods and variables—that is, instantaneous velocity of fiber shortening (Vmax), shortening of contractile elements during isovolumetric contraction (V_{CE}) or Vcf in relation to tension, force or wall stress in isolated cat papillary muscle, intact heart models, in animal studies and in studies in adult subjects (22–32)—consistently found a curvilinear force-velocity relationship. And although the methods and variables used are different (i.e., instantaneous velocity of muscle and mean velocity of fiber shortening are not identical, and tension during isovolumetric contraction and end-systolic wall stress are not identical), we believe that the curvilinear nature of the stress-velocity established with currently used methods supports the hypothesis that the fiber velocity of the normal heart increases exponentially at low afterload in a similar way as does the force-velocity relationship of the intact heart and the isolated cardiac and skeletal muscle analogous to Hill's experimental model (32).

Study limitations. Sodium nitroprusside is a NO-donor with vasodilator effects. Until recently it was assumed that nitroprusside did not have any positive or negative direct inotropic effect. Recent studies investigating the effect of NO on the myocardium without interference of the vasodilator properties have shown that low doses of NO (and thus nitroprusside) have a limited positive inotropic effect, but higher doses have a negative inotropic effect (33–35). It seems unreasonable to believe that the increase of VcFc at low afterload could be partly due to a direct increase in contractility by a positive inotropic action of nitroprusside, especially at the higher doses of 5 and 10 μg/kg/min.

Conclusions. In young piglets and in adult pigs, the relationship between systolic wall stress and VcFc is different in states of low afterload as compared with normal or high afterload. The nature of the relationship seems to be curvilinear.

Combining these results with human data suggests that, analogous to the force-velocity relation of isolated muscle, lowering afterload beyond a critical level alone is responsible for a much more important increase in VcFc than expected from the linear stress-velocity relation established by current methods in both older children and young adults.

This should be taken into account from a practical view when establishing references for the stress-velocity relation, both in infancy and during low-dose dobutamine stress echocardiography. This curvilinear relationship could explain some of the "hypercontractile" states found in low afterload situations as in infancy.

Reprint requests and correspondence: Dr. Daniël De Wolf, Department of Pediatrics, Division of Pediatric Cardiology, University Hospital UZGhent, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: daniel.dewolf@rug.ac.be.

REFERENCES

1. Sahn DJ, De Maria A, Kisslo J. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
2. Lipshultz SE, Orav EJ, Sanders SP, McIntosh K, Colan SD. Limitations of fractional shortening as an index of contractility in pediatric patients infected with human immunodeficiency virus. J Pediatr 1994;125:563–70.
3. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715–24.
4. Colan SD, Sanders DP, Ingelfinger JR, Harmon W. Left ventricular mechanics and contractile state in children and young adults with end-stage renal disease: effect of dialysis and renal transplantation. J Am Coll Cardiol 1987;10:1085–94.
5. Colan SD, Fuji A, Borow KH, MacPherson D, Sanders SP. Noninvasive determination of systolic, diastolic and end-systolic blood pressure in neonates, infants and young children: comparison with central aortic pressure measurements. Am J Cardiol 1983;52:867–70.
6. Colan SD, Borow KM, MacPherson D, Sanders SP. Use of the indirect axillary pulse tracing for noninvasive determination of ejection time, upstroke time, and left ventricular wall stress throughout ejection in infants and young children. Am J Cardiol 1984;53:1154–8.
7. Franklin RC, Wyse RK, Graham TP, Gooch VM, Deanfield JE. Normal values for noninvasive estimation of left ventricular contractile state and afterload in children. Am J Cardiol 1990;65:505–10.
8. Kimball TR, Daniels SR, Khoury P, Meyer RA. Age-related variation in contractility estimate in patients ≤20 years of age. Am J Cardiol 1991;68:1383–7.
9. Rowland DG, Gutgesell HP. Noninvasive assessment of myocardial contractility, preload, and afterload in healthy newborn infants. Am J Cardiol 1995;75:818–21.
10. Colan SD, Parness IA, Spevak PJ, Sanders SP. Developmental modulation of myocardial mechanics: age- and growth-related alterations in afterload and contractility. J Am Coll Cardiol 1992;19:619–29.
11. De Wolf D, Suys B, Verhaaren H, Matthys D, Taeymans Y. Low-dose dobutamine stress echocardiography in children and young adults. Am J Cardiol 1998;81:895–901.
12. Banerjee A, Brook MM, Klautz RJM, Teitel DF. Nonlinearity of the left ventricular end-systolic wall stress-velocity of fiber shortening relation in young pigs: a potential pitfall in its use as a single-beat index of contractility. J Am Coll Cardiol 1994;23:514–24.
13. Grossman W, Jones D, McLaurin P. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.
14. Vaca G, Vono P. The primary reflex effects of distension of the stomach on heart rate, arterial pressure and left ventricular contractility in the anaesthetized pig. Eur J Physiol 1993;425:248–55.
15. Einstein R, Abdul-Hussein N, Wong TW, Chang DHT, Matthews R, Richardson DP. Cardiovascular actions of dopexamine in anaesthetized and conscious dogs. Br J Pharmacol 1994;111:199–204.
16. De Wolf D, Matthys D, Verhaaren H, Sluysmans T. Influence of age and low afterload on the stress-velocity relation of the left ventricle. Pediatr Res 1998;44:600–6.

17. De Wolf D, Suys B, Maurus R, et al. Dobutamine stress echocardiography in the evaluation of late anthracycline cardiotoxicity in childhood cancer survivors. Pediatr Res 1996;39:504–12.
18. Borow K, Lang R, Neumann A, Carroll J, Rajfer S. Physiologic mechanisms governing hemodynamic responses to positive inotropic therapy in patients with dilated cardiomyopathy. Circulation 1988;77:625–37.
19. Borow K, Neumann A, Arensman F, Yacoub M. Left ventricular contractility and contractile reserve in humans after cardiac transplantation. Circulation 1985;71:866–72.
20. Borow K, Green L, Grossman W, Braunwald E. Left ventricular end-systolic stress-shortening and stress-length relations in humans. Am J Cardiol 1982;50:1301–8.
21. Municino A, de Simone G, Roman M, et al. Assessment of left ventricular function by meridional and circumferential end-systolic stress/minor-axis shortening relations in dilated cardiomyopathy. Am J Cardiol 1996;78:544–9.
22. Kreulen T, Bove A, McDonough M, Sands M, Spann J. The evaluation of left ventricular function in man. Circulation 1975;51:677–88.
23. Parmley W, Chuck L, Sonnenblick E. Relation of Vmax to different models of cardiac muscle. Circ Res 1972;30:34–43.
24. Ross J, Covell J, Sonnenblick E. The mechanics of left ventricular contraction in acute experimental cardiac failure. J Clin Invest 1967;46:299–312.
25. Covell J, Ross J, Sonnenblick E, Braunwald E. Comparison of the force-velocity relation and the ventricular function curve as measures of the contractile state of the intact heart. Circ Res 1966;19:364–72.
26. Brutsaert D, Parmley W, Sonnenblick E. Effects of various inotropic interventions on the dynamic properties of the contractile elements in heart muscle of the cat. Circ Res 1970;27:513–22.
27. Glick G, Sonnenblick E, Braunwald E. Myocardial force-velocity relations studied in intact unanesthetized man. J Clin Invest 1965;44:978–88.
28. Levine H, Britman N. Force-velocity relations in intact dog hearts. J Clin Invest 1964;43:1383–96.
29. Levine H, Forward S, McIntyre K, Schechter E. Effect of afterload on force-velocity relations and contractile element work in the intact dog heart. Circ Res 1966;18:729–44.
30. Hugenholtz P, Ellison R, Urschel C, Mirsky I, Sonnenblick E. Myocardial force-velocity relationships in clinical heart disease. Circulation 1970;41:191–202.
31. Sonnenblick E. Contractility in the intact heart: progress and problems. Eur J Cardiol 1974;3/1:319–24.
32. Sonnenblick EH, Parmley WW, Urschel CW. Contractile state of the heart as expressed by force-velocity relations. Am J Cardiol 1969;23:488–503.
33. Prendergast BD, Sagach VF, Shah AM. Basal release of nitric oxide augments the Frank-Starling response in the isolated heart. Circulation 1997;96:1320–9.
34. Yamamoto S, Tsutsui H, Tagawa H, et al. Role of myocyte nitric oxide in β-adrenergic hyporesponsiveness in heart failure. Circulation 1997;95:1111–4.
35. Preckel B, Kojda G, Schlack W, et al. Inotropic effects of glyceryl trinitrate and spontaneous NO donors in the dog heart. Circulation 1997;96:2675–82.